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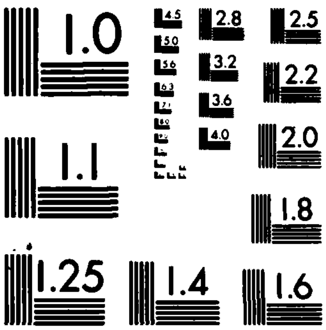

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THE EFFECT OF HYPOTHERMIA ON HEMOSTASIS IN THE BABOON

by

A. J. MELARAGNO, R. C. DENNIS, H. FEINGOLD, A. DOTY, L. COLLINS,

M. L. SCHULZ, W. RIORDAN, L. BELLINI, J. WILLIAMS, L. GUNN,

AND C. R. VALERI

NAVAL BLOOD RESEARCH LABORATORY
BOSTON UNIVERSITY SCHOOL OF MEDICINE
615 ALBANY STREET
BOSTON, MA 02118

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ABSTRACT

The effect of hypothermia on platelet number and function and blood coagulation was studied in baboons cooled to a body temperature of 32 C. During the reduction in body temperature to 32 C, platelet counts were normal and platelet function was normal when assessed by platelet aggregation patterns, platelet dense body content, and release of platelet beta thromboglobulin. Hypothermia to 32 C was associated with a prolonged bleeding time, which was corrected by rewarming to 37 C, but was not associated with increased arterial levels of thromboxane A2 or prostacyclin.

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INTRODUCTION

Accidental hypothermia results from exposure and from cold water immersion.[1-5] Hemorrhage and an increased bleeding tendency occasionally occur, and some instances of disseminated intravascular coagulation (DIC) upon rewarming have been described.[6,7] Hypothermia is sometimes used during surgical procedures, and the potential problems associated with it have been studied by numerous investigators. Harker and associates reported a significant prolongation of the bleeding time when baboons were cooled to a body temperature of between 20 and 30 C, and a correction of the prolonged bleeding time to normal upon rewarming.[8]

A previous study by our laboratory showed a prolonged bleeding time in hypothermic baboons subjected to hypovolemia and hypotension.[9] In the study reported here, baboons that were normovolemic and normotensive were cooled to 32 C to determine if the prolonged bleeding time was due to impaired platelet function, alterations in clotting proteins, or alterations in vascular integrity.

MATERIALS AND METHODS

Five baboons were sedated with Ketamine HCl (Ketaset) and intubated. Each baboon was placed on a mechanical ventilator and given Pavulon, a muscle relaxant. Their ears were plugged with cotton and their eyes were taped shut, a procedure which had been reviewed and approved by the Veterinary Department at Boston University School of Medicine.

A thermal dilution pulmonary artery catheter was placed through a femoral cutdown, and the body temperature was monitored. The extremity temperatures were monitored using cutaneous temperature probes in both upper extremities. Prior to cooling, duplicate baseline measurements of bleeding time were done in both upper extremities. Arterial blood samples were collected through the femoral artery catheter for platelet aggregation studies and for measurements of *coagulation* proteins, beta thromboglobulin, 6 keto PGF1a (stable breakdown product of prostacyclin), thromboxane B2 (stable breakdown product of thromboxane A2), platelet count, hematocrit, hemoglobin, total protein, albumin, and plasma opsonic fibronectin. The baboon was cooled to a body temperature of 32 C using a hypothermic blanket; the skin of one upper extremity was maintained at normal temperature with a heating lamp. When the body core temperature reached 32 C, all measurements were repeated (this sampling period is referred to as "cold initial"). Fifteen minutes after the 32 C temperature was reached, bleeding time measurements were repeated in both upper extremities. After 30 minutes at a body core temperature of 32 C, all measurements were repeated (this sampling period is referred to as "cold 30 minutes"). The baboon was then

rewarmed with a heating blanket and heating lamps, and when the body temperature reached 35 C, all measurements were repeated (this sampling period is referred to as "warm"). All measurements were repeated again once the body temperature had returned to 37 C (this sampling period is referred to as "warm final").

Cardiac output was assessed prior to cooling, after cooling to a body core temperature of 32 C, and after rewarming to a body core temperature of 37 C. About 300 ml of sodium chloride was infused at the time of the cardiac output measurement. The 5 baboons had blood volumes ranging from 858 to 1634 ml, with a mean blood volume of 1166 $\pm$ 318 ml (SD). The blood volume was estimated from the weight of the baboon. The weights ranged from 15.6 to 29.7 kg, and the mean weight was 21 $\pm$ 6 kg (SD). Each baboon was bled 306 $\pm$ 15 ml (SD) of blood and each was infused with 1500 $\pm$ 160 ml of sodium chloride.

Measurements of Platelet Function and Plasma Clotting Proteins

Bleeding times were performed using the automated simplate II bleeding time device (General Diagnostics, Morris Plains, NJ). Capillary pressure was maintained at 40 mm Hg with an inflated blood pressure cuff.

Platelet aggregation studies were performed at 37 C on platelet-rich plasma (PRP) isolated from arterial blood anticoagulated with sodium citrate, 3.8%, in a ratio of 9 parts blood/1 part anticoagulant. Four hundred fifty ul of PRP were treated with 50 ul of ADP (1.0 mM), collagen (1.9 mg/ml), or arachidonic acid (2.5 mg/ml and 5.0 mg/ml with firefly reagent), and platelet aggregation patterns were measured using a lumi-aggregometer (Chronolog Corp., Havertown, PA).

Platelet dense bodies were quantitated by transmission electron micro-

scopy as previously described.[10] The number of dense granules in 100 platelets was quantitated and the number of dense bodies per platelet was determined.

Plasma beta thromboglobulin levels were measured using a commercial radioimmunoassay (Amersham Corp., Arlington Heights, IL). Arterial blood samples were collected in tubes containing EDTA, theophylline, and PGE_1, and were immediately placed in wet ice. Platelet-poor plasma (PPP) was isolated by centrifugation at 1500 X g for 30 minutes at 4 C, and was frozen and stored at -20 C until the assays were performed.

Plasma thromboxane B2 and 6 keto PGF1a were measured using radioimmune assays.[11] The assays were performed on PPP isolated from arterial blood collected in heparin and aspirin, and frozen at -20 C until the assays were performed.

Blood coagulation studies, including activated partial thromboplastin time (aPTT), prothrombin time (PT), Factor VIII (AHF) activity, and thrombin clottable fibrinogen, were performed on PPP isolated from baboon arterial blood collected in 3.8% sodium citrate at a ratio of 9 parts blood/1 part anticoagulant. Human citrated plasma was diluted with sodium chloride to achieve 10, 20, 30 and 40% dilution of the original sodium citrate sample. The coagulation assays were done at 37 C using commercial reagents (General Diagnostics and Dade Scientific). Anti-thrombin III levels were measured by radial immunodiffusion (Calbiochem-Behring, San Diego, CA).

Studies were performed to assess the effect of temperature on platelet aggregation and blood coagulation on baboon and human blood. Platelet aggregation was performed on PRP and coagulation assays were performed on PPP at 30 C and 37 C on blood samples obtained from normal human volunteers and normal baboons.

Total protein and albumin were measured on serum obtained from arterial blood using a Multistat centrifugal analyzer (Instrumentation Laboratory, Lexington, MA).

Plasma opsonic fibronectin levels were measured on PPF isolated from arterial blood collected in K_3EDTA using an immunoturbidometric assay (Boehringer-Mannheim, Indianapolis, IN).

RESULTS

Bleeding Time Measurements

In 5 baboons, bleeding times measured prior to body cooling were similar in both upper extremities. When the body temperature was 37 C, the skin temperature of the upper extremities was 34 C. When the body temperature was cooled to 32 C, the skin temperature was 27.5 C and the bleeding time increased from 4 minutes to 9 minutes. There was a significant prolongation of the bleeding time when the baseline bleeding time was compared to the bleeding time at the cold 15-minute period in the cold arm (paired t-test = 3.23, $p < 0.05$). When a heating lamp was used to externally warm the skin to 35 C, the bleeding time increased from 4 minutes to 6 minutes. When the baboon was rewarmed to 37 C, the bleeding times in both arms returned towards baseline levels. Platelet counts did not change with changes in body temperature (Figure 1).

A bleeding time of 4 minutes was observed when the skin temperature was 34.5 $\pm$ 0.5 C; when the skin temperature was less than or greater than 34.5 $\pm$ 0.5 C, the bleeding time was greater than 4 minutes (Figure 2).

Platelet Aggregation

The in vitro baboon platelet aggregation patterns done at 37 C showed no differences during the cooling and rewarming of the baboon (Table 1).

Platelet aggregation studies performed on both human and baboon platelet-rich plasma showed similar patterns at 30 C and 37 C when the platelets were treated with ADP, collagen or arachidonic acid (Table 2).

Platelet Dense Body and Plasma Beta Thromboglobulin Levels

In three studies, the platelet dense body content did not change during cooling and rewarming (Table 3). The plasma beta thromboglobulin levels did not change significantly during cooling and rewarming, indicating that there was no release of platelet alpha granules.

Plasma Thromboxane B2 and 6 Keto PGF_{1a} Levels

In all five baboon studies, the baseline arterial samples contained the highest levels of plasma thromboxane B2. With each successive sampling period, the level of plasma thromboxane B2 fell, and this reduction was independent of changes in the baboon's body temperature. Measurable levels of plasma 6 keto PGF_{1a} were detected in only 2 of the 5 studies. In these two studies, the baseline samples contained the most plasma 6 keto PGF1a, and there was a marked reduction in the stable breakdown product of prostacyclin after hypothermia was induced. The decrease in thromboxane B2 and 6 keto PGF_{1a} levels may be explained by the dilution of the plasma with sodium chloride solution during the study (Table 4).

Blood Coagulation Studies

A 10 to 20% prolongation of the prothrombin time and activated partial thromboplastin time were observed during cooling and after rewarming (Table 5). In three of the five baboons reported in group A, the fibrinogen level also decreased during cooling and after rewarming. In the two other baboons reported in Group B, the fibrinogen level did not change. The Factor VIII (AHF) activity and anti-thrombin III levels remained relatively constant during the study. The prolonged PT and aPTT, and decreased fibrinogen levels were associated with a 15-25% decrease in hemoglobin and

hematocrit values (Figure 3) and total protein, albumin and plasma opsonic fibronectin levels (Table 6, Figure 4).

In order to assess whether the changes observed were due to dilution as a result of large infusion of sodium chloride solution, studies were performed on plasma diluted with varying amounts of saline. These studies showed that dilution of plasma proteins in vitro produced a prolongation of the PT and aPTT times (Figure 5) and decreases in fibrinogen and Factor VIII levels (Figure 6). In the studies done in the baboons, however, we did not observe decreases in Factor VIII (AHF) activity associated with dilution.

In vitro studies were done to compare PT, aPTT, and thrombin time measurements performed at 30 C with measurements performed at 37 C (Table 7). PT, aPTT and thrombin times were slightly but significantly longer at 30 C than at 37 C ($p < 0.01$).

DISCUSSION

Baboons cooled to 32 C had prolonged bleeding times with normal platelet counts and normal platelet function. Platelet aggregation patterns measured at 37 C were similar prior to, during, and after hypothermia. Aggregation patterns performed at 30 C were similar to those performed at 37 C.

There was no loss of dense bodies during hypothermia and plasma beta thromboglobulin levels did not increase in the baboons during or after hypothermia; these findings suggest that a platelet dysfunction was not induced by the cold.

The results of this study appear to rule out platelet dysfunction or abnormalities in coagulation as the cause of the prolonged bleeding time observed during hypothermia. Thus, the prolonged bleeding time may be due to an alteration in vascular integrity. In the hypothermic baboon, the bleeding time was not prolonged in an extremity when skin temperature was maintained at 34 C.

The etiology of the altered vascular integrity is unclear. When the superficial vessels of the skin are cut while performing a bleeding time, the normal physiologic response of the capillaries is to contract. During hypothermia in man the superficial vessels are vasodilated.[12] Keatinge has demonstrated that sheep arterioles subjected to cold have impaired ability to respond to physiologic stimuli and drugs.[13] The prolonged bleeding time observed during hypothermia may be due to an inability of the dilated superficial vessels to contract to cold after being severed.

The prolongation of the PT and aPTT and reduction in fibrinogen that

was observed at 37 C was related to a dilution of plasma proteins that was a result of withdrawal of blood and the infusion of sodium chloride solution during the study. The PT, aPTT, and thrombin time of normal plasma were slightly but significantly prolonged when they were performed at 30 C compared to 37 C. In our study, the dilution of the plasma with sodium chloride solution can explain the prolonged aPTT, PT and TT.

Our data suggest that the prolonged bleeding times seen in baboons subjected to hypothermia can be reduced by raising the body temperature to normal. This could be important in patients undergoing cardiopulmonary bypass surgery who continue to bleed post-operatively, and further studies should be done in patients to determine whether restoring the skin temperature to normal will stop bleeding.

FIGURE 1

One upper extremity was externally warmed to maintain normal skin temperature and the other extremity was not when the body temperature was reduced to 32 C.

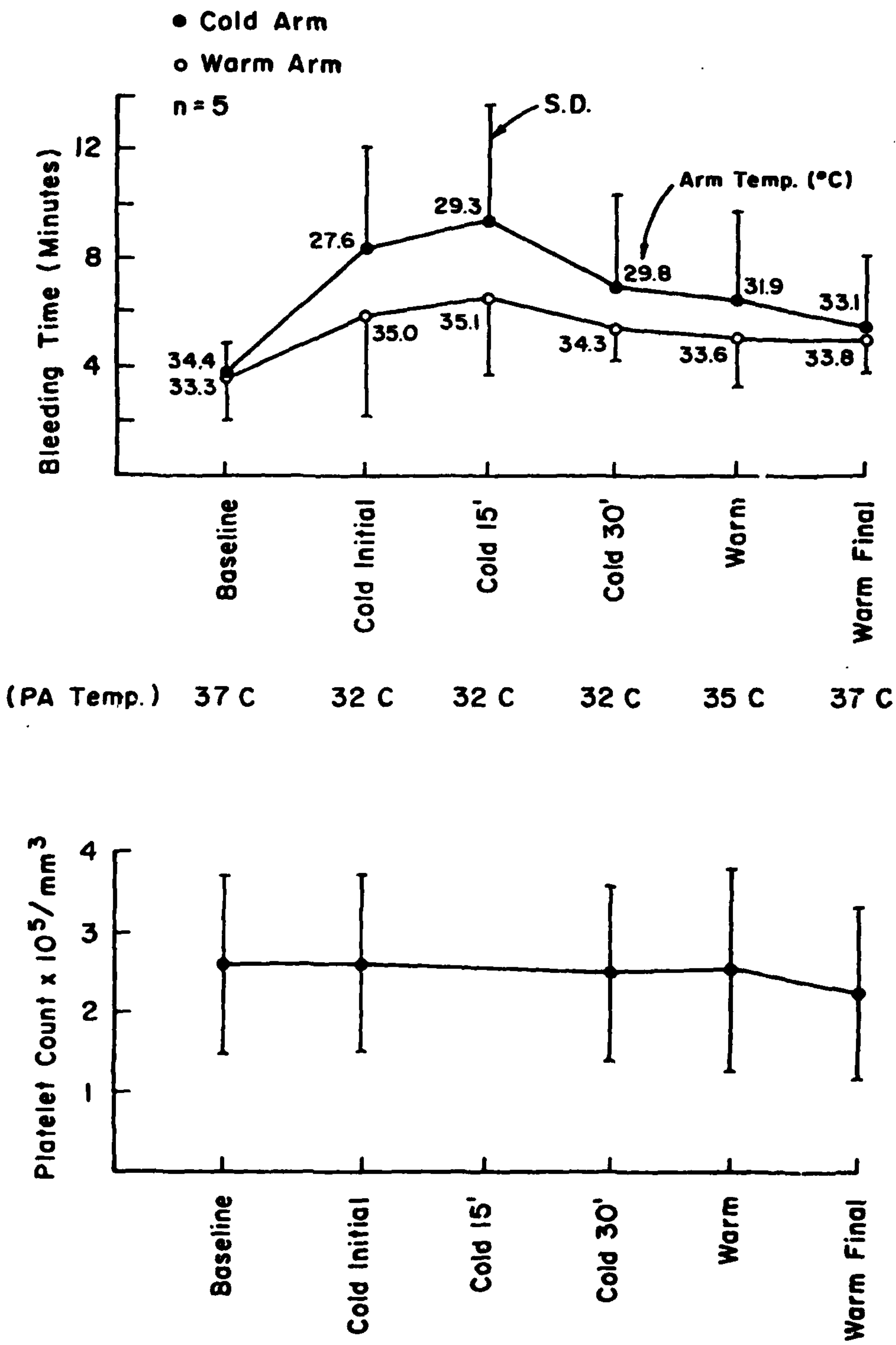

FIGURE 1

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FIGURE 2

The relation between skin temperature and the template bleeding time in the baboon.

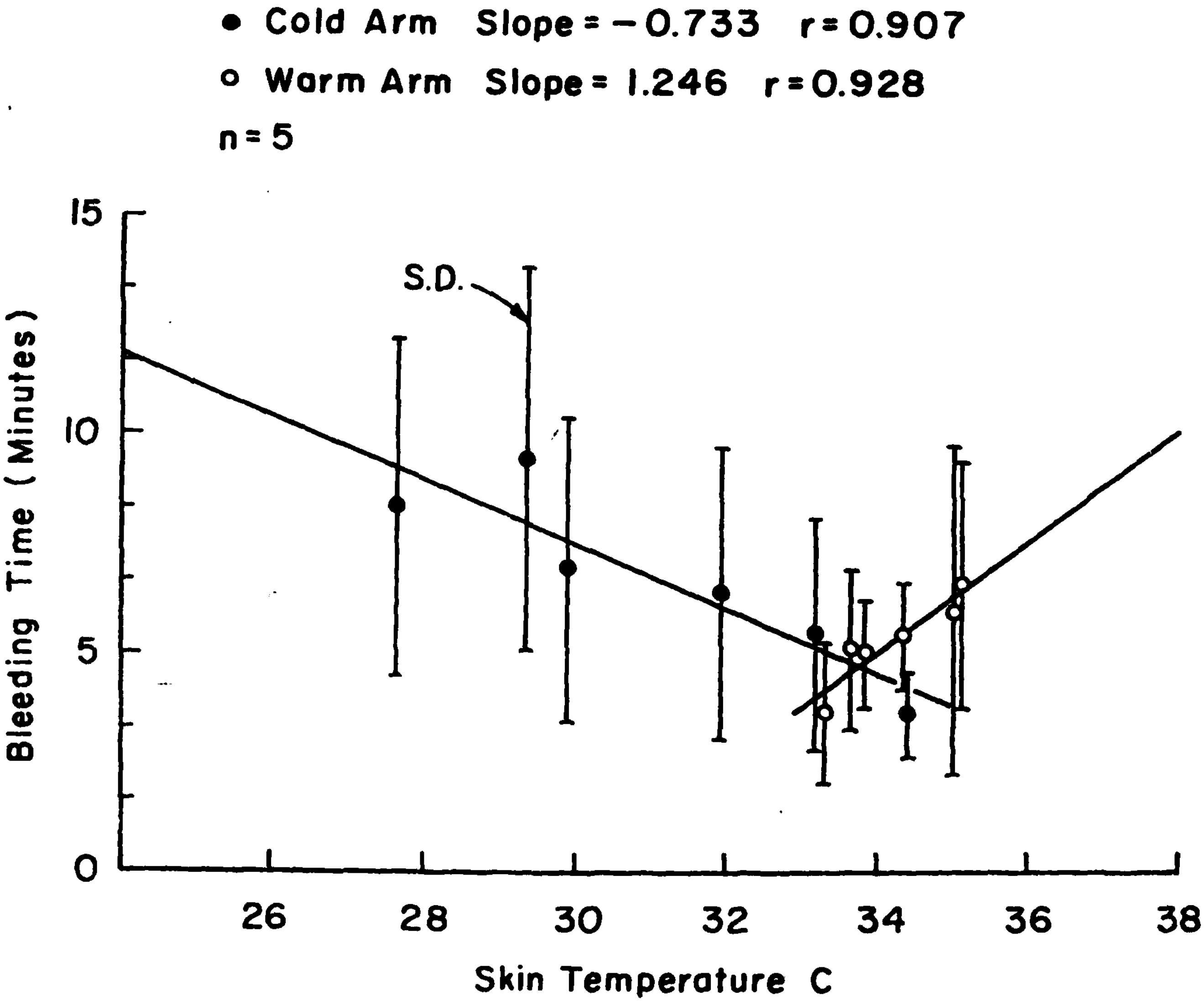

FIGURE 2

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FIGURE 3

Hemoglobin and hematocrit values in baboons cooled to 32 C and rewarmed to 37 C. During the study, about 300 ml of blood was withdrawn and about 1500 ml of sodium chloride solution was infused.

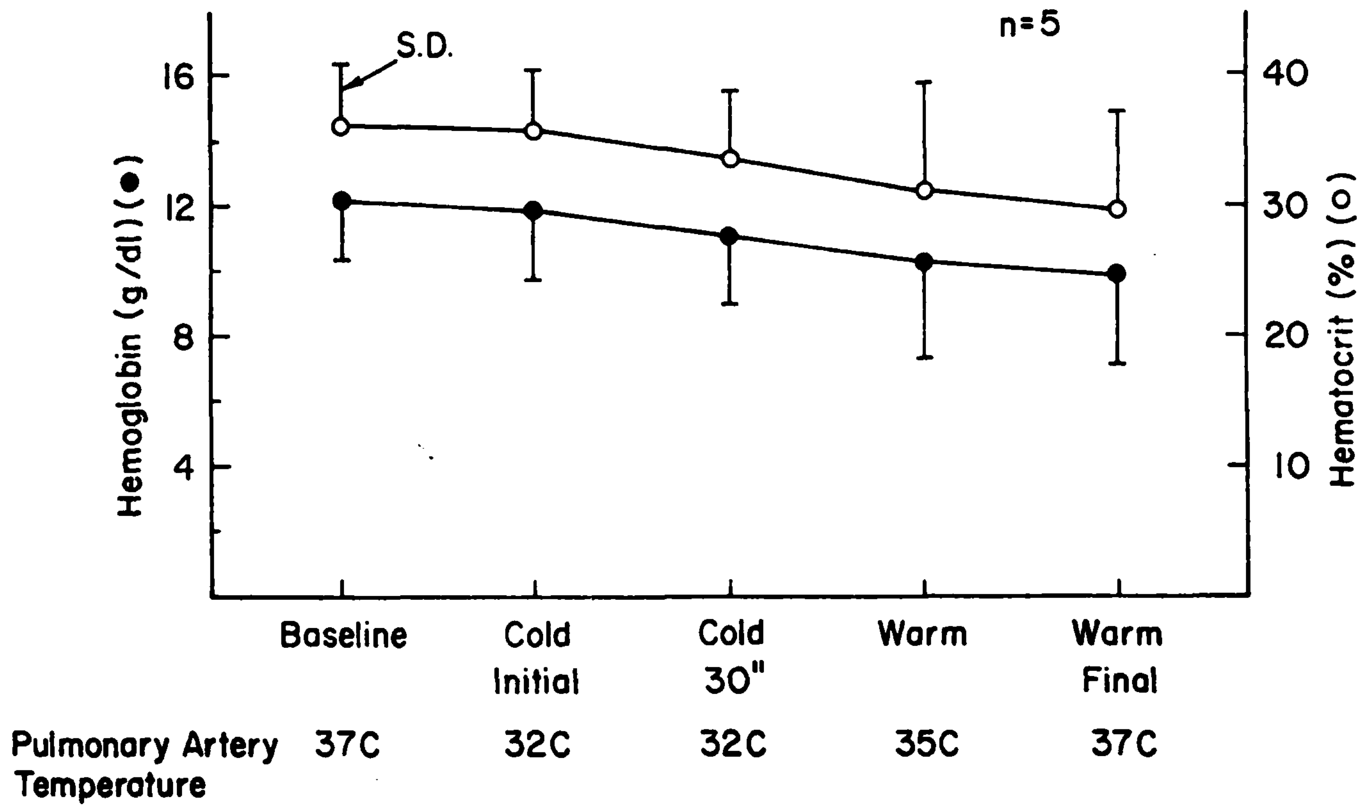

FIGURE 3

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FIGURE 4

The percent change in hemoglobin, hematocrit, and plasma proteins in 5 baboons cooled to 32 C and rewarmed to 37 C. About 300 ml of blood was withdrawn and about 1500 ml of sodium chloride solution was infused during the study.

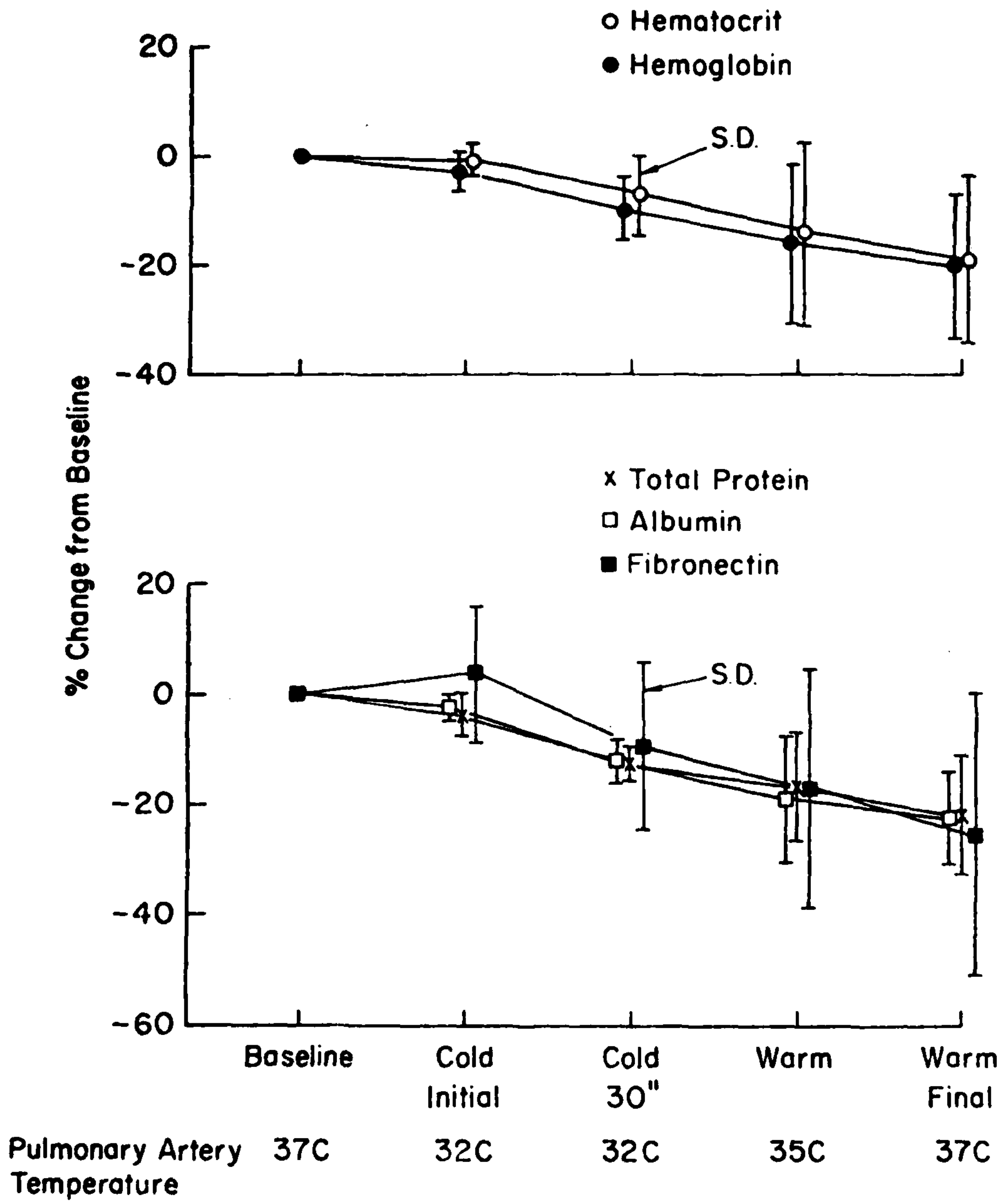

FIGURE 4

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FIGURE 5

Prothrombin time and activated partial thromboplastin time in human citrated plasma diluted with sodium chloride solution.

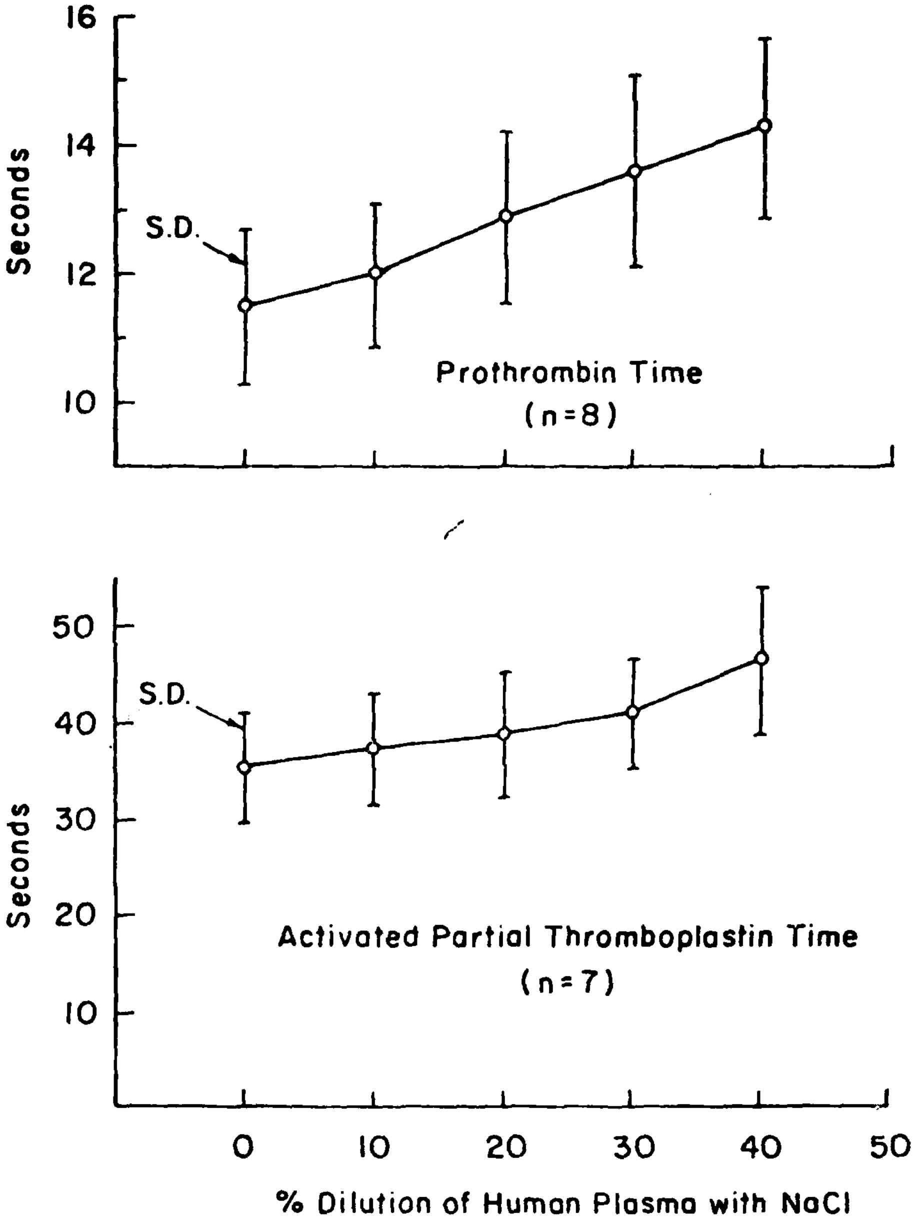

FIGURE 5

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FIGURE 6

Factor VIII (AHF) activity and fibrinogen level in human citrated plasma diluted with sodium chloride solution.

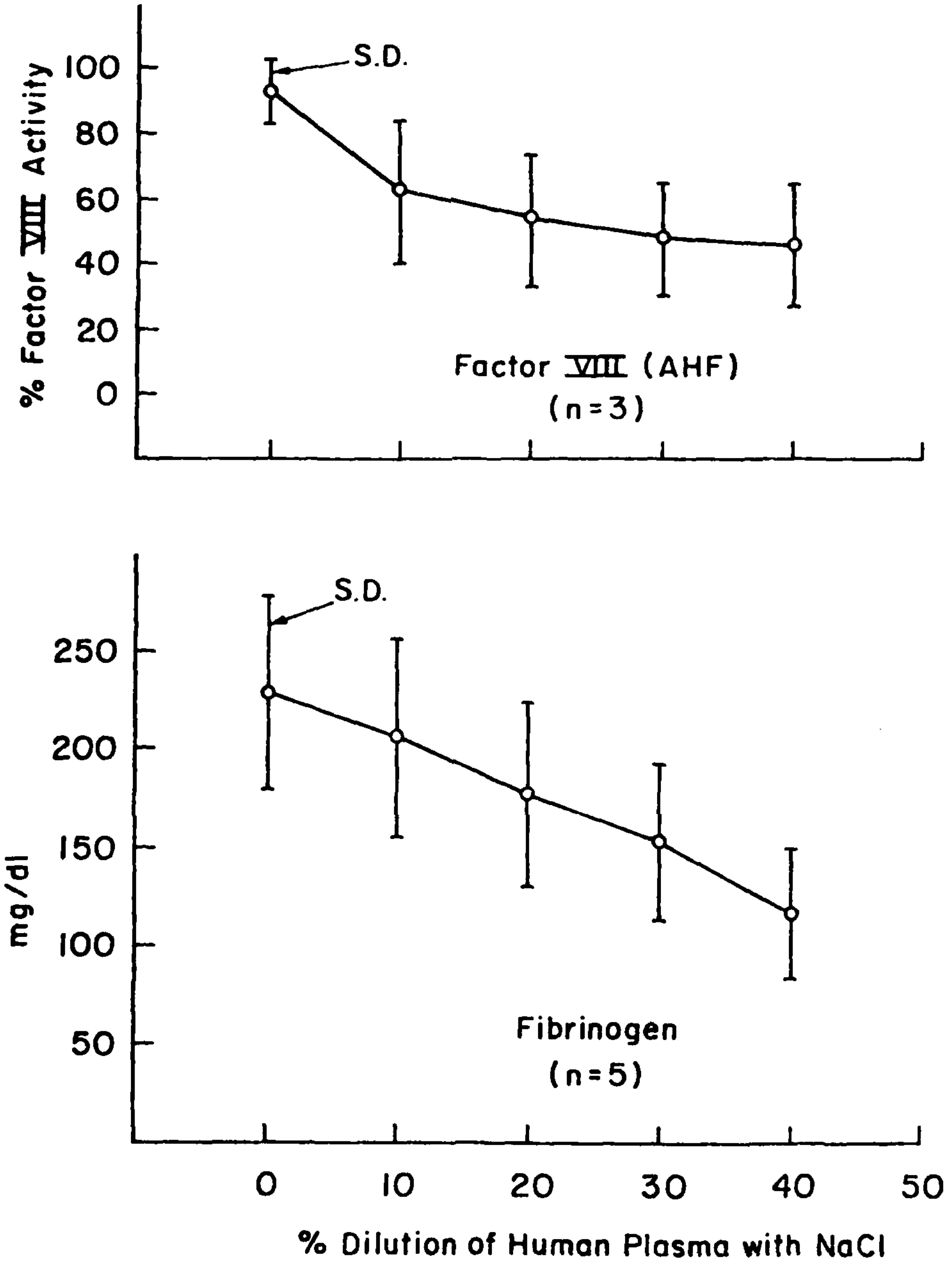

FIGURE 6

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TABLE 1

PLATELET AGGREGATION PATTERNS PERFORMED AT 37 C IN BABOONS COOLED TO 32 C AND REWARMED TO 37 C

BABOON	SAMPLE TIME	BODY TEMP. (C)	COLLAGEN 1.9 mg/ml	ADP 1.0 mM	ARACHIDONIC ACID WITH FIREFLY EXTRACT 2.5 or 5.0 mg/ml
56	BASELINE	37	0*	4	1**
	COLD INITIAL	32	0*	4	1**
	COLD 30 MINUTES	32	0*	4	1**
	WARM	35	0*	4	1**
	WARM FINAL	37	0*	4	1**
69	BASELINE	37	4	4	4
	COLD INITIAL	32	4	4	4
	COLD 30 MINUTES	32	4	4	4
	WARM	35	4	4	4
	WARM FINAL	37	4	4	4
68	BASELINE	37	4	4	[illegible]
	COLD INITIAL	32	4	4	4
	COLD 30 MINUTES	32	4	4	4
	WARM	35	4	4	4
	WARM FINAL	37	-	4	4
107	BASELINE	37	4	4	4
	COLD INITIAL	32	4	4	4
	COLD 30 MINUTES	32	4	4	4
	WARM	35	4	-	-
	WARM FINAL	37	-	-	-
79	BASELINE	37	4	4	4
	COLD INITIAL	32	4	4	4
	COLD 30 MINUTES	32	4	4	4
	WARM	35	4	4	4
	WARM FINAL	37	4	4	4

AGGREGATION CODE

4 - full aggregation
3 - biphasic aggregation
2 - primary without secondary aggregation
1 - aggregation/disaggregation
0 - no aggregation

*Laboratory-prepared collagen
**Firefly extract not used

TABLE 2

IN VITRO PLATELET AGGREGATION STUDIES AT 30 C AND 37 C USING HUMAN AND BABOON PLATELETS

DONOR	COLLAGEN 1.9 mg/ml 37 C	30 C	ADP 1.0 mM 37 C	30 C	ARACHIDONIC ACID 5 mg/ml WITH FIREFLY EXTRACT 37 C	30 C
HUMAN #1	4	4	4	4	4	4
HUMAN #2	4	4	4	4	4	4
HUMAN #3	4	4	4	4	4	4
HUMAN #4	4	4	4	4	0	4
BABOON #1	4	4	4	4	4	4
BABOON #2	4	4	4	4	0	0

AGGREGATION CODE

4 - full aggregation
3 - biphasic aggregation
2 - primary aggregation without secondary aggregation
1 - full aggregation with disaggregation
0 - no aggregation

TABLE 3

PLATELET DENSE BODY CONTENT AND PLASMA BETA THROMBOGLOBULIN LEVELS IN BABOONS COOLED TO 32 C AND REWARMED TO 37 C (MEAN ± SD)

SAMPLE TIME	BODY TEMPERATURE (C)	DENSE BODIES PER PLATELET (n = 3)	PLASMA BETA THROMBOGLOBULIN (ng/ml) (n = 5)
BASELINE	37	11.8 ± 2.2	48.2 ± 7.6
COLD INITIAL	32	11.1 ± 3.3	40.8 ± 6.8
COLD 30 MINUTE	32	12.7 ± 3.1	43.8 ± 8.3
WARM	35	12.8 ± 4.5	41.0 ± 6.0
WARM FINAL	37	12.2 ± 3.2	39.8 ± 11.0

TABLE 4

ARTERIAL PLASMA THROMBOXANE B2 AND 6-KETO PGF_{1a} LEVELS IN BABOONS COOLED TO 32 C AND REWARMED TO 37 C

BABOON	SAMPLE TIME	BODY TEMP (C)	PLASMA THROMBOXANE B2 (ng/ml)	PLASMA 6-KETO PGF_{1a} (ng/ml)	RATIO TxB2/6-keto PGF_{1a}
56	BASELINE	37	0.220	0	-
	COLD INITIAL	32	0.165	0	-
	COLD 30 MINUTES	32	0.115	0	-
	WARM	35	0.031	0	-
	WARM FINAL	37	0.080	0	-
69	BASELINE	37	0.660	<0.037	>17.8
	COLD INITIAL	32	0.175	<0.037	>4.7
	COLD 30 MINUTES	32	0.040	<0.037	>1.1
	WARM	35	0.125	<0.037	>3.4
	WARM FINAL	37	0.105	<0.037	>2.8
68	BASELINE	37	0.215	0.560	0.38
	COLD INITIAL	32	0.056	0.052	1.08
	COLD 30 MINUTES	32	0.105	0.052	2.20
	WARM	35	0.215	0.530	0.41
	WARM FINAL	37	0.017	0.037	0.46
107	BASELINE	37	0.340	1.100	0.31
	COLD INITIAL	32	0.080	0.060	1.33
	COLD 30 MINUTES	32	0.080	0.070	1.14
	WARM	35	0.012	0.060	0.20
	WARM FINAL	37	0.050	0.310	0.16
79	BASELINE	37	0.115	0	-
	COLD INITIAL	32	0.1	0	-
	COLD 30 MINUTES	32	0.1	0	-
	WARM	35	0.1	0	-
	WARM FINAL	37	0.1	0	-

TABLE 5

COAGULATION PROTEINS IN BABOONS IN GROUPS A AND B COOLED TO 32 C AND REWARMED TO 37 C (MEAN ± SD)

SAMPLE TIME	BODY TEMPERATURE (C)	n	PROTIME (sec)	aPTT (sec)	FACTOR VIII (AHF) % ACTIVITY	FIBRINOGEN (mg/dl)	ANTI-THROMBIN III (mg/dl)
				GROUP A			
BASELINE	37	3	13.8 ± 0.5	39.6 ± 10.0	64.7 ± 31.4	335 ± 204	31.3 ± 26.5
COLD INITIAL	32	3	13.7 ± 0.6	41.5 ± 11.0	67.0 ± 35.8	313 ± 227	34.3 ± 6.0
COLD 30 MINUTES	32	3	15.2 ± 1.5	44.5 ± 10.6	44.2 ± 7.90	280 ± 182	35.3 ± 18.2
WARM	35	3	15.2 ± 2.5	44.9 ± 10.7	59.5 ± 26.1	215 ± 230	39.8 ± 17.6
WARM FINAL	37	3	16.4 ± 3.4	42.7 ± 7.6	67.3 ± 53.2	257 ± 202	34.3 ± 19.9
				GROUP B			
BASELINE	37	2	14.9 ± 1.0	37.4 ± 3.4	46.5 ± 16.3	102 ± 26	35.8 ± 4.6
COLD INITIAL	32	2	14.8 ± 0.9	41.4 ± 9.1	51.5 ± 16.3	126 ± 48	35.3 ± 6.7
COLD 30 MINUTES	32	2	16.1 ± 2.0	45.3 ± 11.7	45.5 ± 17.7	133 ± 88	46.0 ± 2.2
WARM	35	2	17.4 ± 3.4	44.9 ± 12.3	52.0 ± 2.80	109 ± 71	34.0 ± 9.9
WARM FINAL	37	-	-----	-----	-----	-----	-----

TABLE 6

TOTAL PROTEIN, ALBUMIN, AND PLASMA ONCOTIC FIBRONECTIN IN BABOONS COOLED TO 32 C AND REWARMED TO 37 C (n = 5) (MEAN ± SD)

SAMPLE TIME	TEMPERATURE (C)	TOTAL PROTEIN (g/dl)	ALBUMIN (g/dl)	FIBRONECTIN (ug/ml)
BASELINE	37	6.09 ± 0.93	2.81 ± 0.49	223 ± 55.5
COLD INITIAL	32	5.87 ± 1.07	2.74 ± 0.49	231 ± 57.4
COLD 30 MINUTES	32	5.35 ± 0.85	2.49 ± 0.52	201 ± 54.1
WARM	35	5.10 ± 1.17	2.31 ± 0.63	186 ± 64.6
WARM FINAL	37	4.79 ± 1.09	2.20 ± 0.53	164 ± 57.1

TABLE 7

PROTHROMBIN TIME, ACTIVATED PARTIAL THROMBOPLASTIN TIME, AND THROMBIN TIME IN NORMAL BABOONS MEASURED AT 30 C AND 37 C (MEAN ± SD)

TEST	n	30 C	37 C	PAIRED T-TEST
PROTHROMBIN TIME (sec)	13	14.4 ± 3.5	13.2 ± 2.4	$p < 0.01$
ACTIVATED PARTIAL THROMBOPLASTIN TIME (sec)	12	37.9 ± 8.8	34.8 ± 7.8	p 0.01
THROMBIN TIME (sec)	12	10.4 ± 2.3	9.7 ± 2.3	$p < 0.01$

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